Remarks/Argument

This paper is being filed in response to the Office Action mailed September 25, 2006 with regards to the Sections 101 and 112 rejections contained therein.

Response to the Section 101 rejection

Claims 1, 7, 8 and 10 are rejected under 35 U.S.C. § 101 as failing to comply with the utility requirement because the claimed invention is allegedly "not supported by either a specific and substantial asserted utility or well-established utility." The Applicants respectfully traverse this rejection.

A claimed invention meets the utility requirements of § 101 if one skilled in the art would appreciate why such an invention is useful and if the utility is credible, specific, and substantial. *Utility Examination Guidelines*, 66(4) F.R. 1092, 1098, January 5, 2001. Credibility is assessed from the perspective of one of ordinary skill in the art, in view of the disclosure and any other evidence of record (*e.g.,* test data) that is probative of the applicant's assertions. Specific and substantial utility requirements are satisfied if the applicant discloses at least one particular practical purpose.

Here, the Applicants assert that the decrease in BRCC-2 expression upon treatment with Raf-antisense oligonucleotides, as demonstrated in Figure 5, indicates "a link between the novel BRCC-2 gene and a known apoptosis pathway." The conclusion that BRCC-2 is a component of the cell survival/cell death pathway is based on experimental data set forth in the specification and is further verified by a post-filing, peer-reviewed publication (See Broustas et al., 2004; copy enclosed). Thus, the Applicants' disclosure and test data are probative of the Application's assertions and demonstrate the credible utility of the invention.

Apoptosis is an evolutionarily conserved pathway for programmed cell death. The disruption of apoptosis is implicated in many diseases, such as cancer, auto-immune disorders, and neurodegeneration. Since treating and identifying cancer and other diseases associated with apoptosis is a desirable outcome based upon need in the art, a gene that mediates apoptosis has practical "real world use" for the diagnosis and therapeutic treatment of diseases by the methods set forth in the specification. Thus, genes that play a role in the apoptopic pathway, such as those recited in claims 1, 7, 8 and 10 are considered to have substantial utility.

The Applicants' disclosure discusses several uses of BRCC-2 related to the apoptotic pathway. For example, the detection of expression of the BRCC-2 gene (pg. 25), synthesis of antibodies (pg. 31) or identification of new cancer therapy targets (pg. 39), among other applications discussed in the specification. These uses indicate particular and specific utilities of the invention.

In light of the foregoing, one skilled in the art would appreciate that the uses of BRCC-2 listed on pages 4 and 5 of the specification describe credible, specific, and substantial utilities. For example, BRCC-2 can be used to make anti-sense molecules and antibodies for the detection and treatment of cancers associated with abnormal apoptosis regulation by the methods described on pages 20-22 and 33-35. Thus, claims 1, 7, 8 and 10 meet the utility requirements of § 101, because the disclosure demonstrates at least one credible, specific, and substantial utility of the invention.

Page 9 of the Office Action asserts the data presented in Figure 5, along with the relevant portions of the specification, allegedly do not show that the BRCC-2 gene is involved in apoptosis, and thus does not support the asserted utility. Specifically, the Office Action states that concomitant decrease in expression of Raf-1 and another gene does not indicate that the BRCC-2 gene plays a role in apoptosis. In support of this argument, the Examiner cited Patel et al., which employs an experimental protocol similar to one discussed in Applicants' specification; namely, the use of Raf-1 anti-sense oligonucleotides to identify differentially expressed genes and the generation of an expression profile in multiple tissues and cancer cell types. Patel et al. identified two novel genes and suggested that (emphasis added) "their expression in multiple tissues and cancer cell lines indicates their ***possible*** housekeeping function (Patel et al., 1997; pg. 682)." The Examiner maintains that because Patel et al. assumed the novel genes were merely housekeeping genes, there is no reason to believe that the BRCC-2 polynucleotide is not also a housekeeping gene.

The assumption in the Office Action concerning the significance of the ubiquitously expressed genes set forth in Patel et al. is immaterial to determining the utility of the present application. Indeed, the Patel et al. document, which was co-authored by a co-inventor of this application, stated that biological significance of the genes discussed therein remained to be determined, suggesting that the possible apoptotic function of these genes had not been ruled out.

Patel et al. never positively indicated that the subject matter recited in the claims lacks the asserted utility. Therefore, Patel et al. it does not provide substantial grounds to question the credibility of the presently asserted utility.

Additionally, the Examiner argues that the *in vitro* model disclosed in the specification does not adequately support the assertion of therapeutic utility in the absence of substantiating *in vivo* data. Specifically, on page 9 of the Office Action, Gura was cited to convey how *in vitro* methods are allegedly not predictive of therapeutic effects.

The Applicants, however, note that many publications from the time the application was filed indicate that *in vivo* models suffer considerable shortcomings, thus underscoring the value of *in vitro* models. Indeed, it is stated within the Gura article that twelve currently used therapies failed to elicit a significant response in 62.5% of the *in vivo* models tested. In comparison, the high predictive value of *in vitro* methods was highlighted by a study that compiled data from 2,300 *in-vitro/in-vivo* correlations collected from a 12-year period (See Von Hoff, 1990; copy enclosed). This document indicates that *in vitro* methods are predictive of 69% true positives and 91% true negatives. Furthermore, a more recent bioinformatic analysis compared the predictive value of *in vitro* and *in vivo* methods for treatment of solid tumors. This study indicated that "the *in vitro* cell line model is of, at least, equivalent usefulness to the human xenograft model" and that both methods were "more predictive than the murine allograft model" (See Voskoglou-Nomikos et al., 2003 hereafter referred to as "Voskoglou-Nomikos"; copy enclosed).

Thus *in vitro* methods can provide an indication of pharmacological activity relevant to pharmacological use, when the *in vivo* methods fail to do so. The limitations of *in vivo* models as discussed in Gura and Voskoglou-Nomikos underscore the importance of considering *in vitro* models when assessing the utility of a potential therapy. Consequently, the Examiner's assertion that *in vitro* data alone cannot positively identify therapeutic activity is insufficient to sustain the utility rejection. Indeed, *in vitro* models are accepted in the art as being reasonably predictive of therapeutic utility.

To further support the assertion that *in vitro* data alone is insufficient to impart a substantial utility, the Office Action cited *In Re Brana* as an example of previous case law in which *in vivo* evidence was ruled necessary and sufficient to support an asserted therapeutic utility. The Office Action states that the Applicants of *In Re Brana* demonstrated the utility of the claimed compound because they disclosed *in vivo* evidence of treatment of tumors in mice by both the claimed invention and structurally analogous compounds.

However, consideration of Voskoglou-Nomikos counters the position that the *in vitro* model of the present application is inadequate and the *in vivo* data, such as the data presented in *In Re Brana,* is necessary to support the asserted utility. More specifically, Voskoglou-Nomikos questions the allegedly superior predictive value of the experimental methods that support a utility as asserted in *In Re Brana.*

The *in vivo* method disclosed in the underlying application of *In Re Brana* consisted of murine models injected with two cultured cell lines of lymphocytic leukemia. This experimental method is similar to the murine allograft model that was deemed by Voskoglou-Nomikos to be less predictive of clinical value than *in vitro* cell line models. Indeed, the authors stated that "the murine allograft model in drug development may not be justified," whereas they argued for "emphasis to be placed on *in vitro* cell lines."

While the Voskoglou-Nomikos publication was particularly concerned with solid tumors (as opposed to *In Re Brana,* which involved hematological malignancies), this document underscores the liability of wholesale disregard for *in vitro* data. Furthermore, it indicates that there is no reason to believe that *in vivo* methods have a comprehensively superior predictive value compared to *in vitro* methods in either solid or blood-related tumors. Consequently, one skilled in the art would recognize the asserted utility of the present application because it is supported by a model that is at least as predictive as that of *In Re Brana.*

The Office Action also discussed *Brenner vs. Manson*, 148 U.S.P.Q. 689 (1966). The Office Action asserted that this application is analogous to *Brenner* because it allegedly claims that a compound structurally analogous to therapeutic agents possesses the same activity. However, the present application demonstrates the role of the BRCC-2 gene in apoptosis by test data, and thus experimentally establishes the role of the isolated BRCC-2 gene as claimed. Indeed, the application establishes a demonstrated interaction of the invention with a protein involved in apoptosis, which is a recognized therapeutic target-pathway. Furthermore, the rejected claims recite the isolated nucleotide molecule comprised of a sequence identical to the BRCC-2 gene. Therefore, the claimed molecule is not merely structurally analogous to a therapeutic agent, it is *comprised* of a therapeutic agent. Since the asserted utility of the present application is supported by direct experimental evidence, rather than mere structural similarity to known therapeutic agents, this application is not analogous to *Brenner vs. Manson.*

Furthermore, the asserted utility of the invention was demonstrated in successful practice, precisely as recited in claims 1, 7, 8, 10, and 44, in a post-filing publication authored by the inventors (See Attached Broustas et al., 2004). In this publication, the BRCC-2 gene was ectopically expressed in three cell lines and shown to induce apoptosis by DNA fragmentation and enhanced numbers of cells in the sub-G_1 phase. It was further determined that the N-terminal BH3-like domain of BRCC-2 was responsible for apoptosis in a Caspase-dependent manner. These data verify the assertion of utility set forth in the present application, that the claimed molecule possesses a substantial role in apoptosis. As discussed above, one skilled in the art would recognize that numerous diseases associated with apoptosis lend specific "real world uses" to the invention in the form of diagnostic screenings and potential therapies involving the BRCC-2 gene. These real world uses are disclosed in the specification in paragraphs [0015] – [0023] which discuss the use of a molecule isolated from the BRCC-2 gene as anti-sense molecules or antibodies for the detection of the abnormal regulation of apoptosis that is characteristic of cancer and treatment thereof.

The role of the BRCC-2 gene as an apoptotic mediator and the diagnostic and potential therapeutic applications thereof demonstrate the credible, specific, and substantial utility of the present invention. Claims 1, 7, 8, and 10 therefore satisfy the requirements of § 101.

Response to the section 112, 1st paragraph rejection

Claims 1, 7, 8 and 10 are rejected under 35 U.S.C. §112, first paragraph. This rejection follows from and is dependent upon the §101 rejection discussed above. That is, one skilled in the art would allegedly not be enabled to use the claimed invention "in any substantial manner with the expectation of success" because an appropriate utility has allegedly not been established. For the reasons set forth above, the application does, in fact, describe sufficient specific, substantial and credible utilities for the claimed isolated polynucleotide of the BRCC-2 gene. One skilled in the art would therefore know how to make and use the claimed invention.

The Applicants therefore respectfully requested that the §112, 1st paragraph enablement rejection of Claims 1, 7, 8 and 10 be withdrawn.

Based on the foregoing, the Applicants respectfully submit that the Application is in a condition for allowance, which is respectfully requested.

Respectfully submitted,
Paul Carango

Paul Carango
Reg. No. 42,386
Attorney for Applicants

PC:
(215) 656-3320